Pharmacokinetics (PK) of Voxelotor (GBT440) Using Population Pharmacokinetic (PPK) and Physiologically Based Pharmacokinetic (PBPK) Modeling in Pediatric Subjects With Sickle Cell Disease

Carla B. Washington, PhD; Michelle Green, PhD; Adlette C. Inati, MD; Jeremie H. Estepp, MD; Clark Brown, MD, PhD; Robert Austin, MD, PhD; Erica Fong, MBA; Athiwat Hutchaleelaha, PhD; Margaret E. Tonda, PharmD; Josh Lehrer, MD, MPhil, FACC; Florin Spiridon, MD, PhD; Hanjie Hsu, MD, PhD; Robert Liem, MD; Connie Piccone, MD; Winfred Wang, MD; Gerald M. Woods, MD; Sandra Dixon, MS; Pratshant Patel, Ph.D.; Anya D. Nwando, BSc; Radhika Rana, MSc; Eric Fong, MBA; Athiwat Hutchaleelaha, PhD; Margaret E. Tonda, PharmD; Josh Lehrer, MD, MPhil, FACC; Florin Spiridon, MD, PhD; Hanjie Hsu, MD, PhD; Robert Liem, MD; Connie Piccone, MD; Winfred Wang, MD; Gerald M. Woods, MD; Sandra Dixon, MS; Pratshant Patel, Ph.D.; Anya D. Nwando, BSc; Radhika Rana, MSc; and the Global Blood Therapeutics GBT440 Pediatric Studies Team.

BACKGROUND

Sickle cell disease (SCD) is an autosomal recessive disorder caused by a mutation in the β-globin chain of the hemoglobin (Hb) molecule resulting in unstable HbS that readily Polymerization (HbSS) and the related sickle transfused into the peripheral circulation results in vaso-occlusion, sickling, hemolysis, and organ damage. People with SCD have 2 β-globin chains (β0 thalassemia) that are replaced by abnormalities that create non-β-globin chains and produce abnormal HbS, which polymerize, resulting in a sickle cell trait (HbAS) or sickle cell disease (HbSS).

Voxelotor (GBT440) is a small molecule that preferentially binds to the δ-chain of HbS. In a Phase 2 study, voxelotor improved hemoglobin oxygen affinity in patients with sickle cell anemia (HbSS). Voxelotor is currently in Phase 3 trials for the treatment of pediatric SCD and sickle cell trait. In Phase 3 trials, voxelotor was safe and well tolerated in children and adolescents with SCD.

METHODS

Carla B. Washington, PhD1; Michelle Green, PhD2; Adlette C. Inati, MD3; Jeremie H. Estepp, MD4; Clark Brown, MD, PhD5; Robert Austin, MD, PhD6; Erica Fong, MBA1; Athiwat Hutchaleelaha, PhD1; Margaret E. Tonda, PharmD1; Josh Lehrer, MD, MPhil, FACC7; Florin Spiridon, MD, PhD8; Hanjie Hsu, MD, PhD9; Robert Liem, MD10; Connie Piccone, MD11; Winfred Wang, MD12; Gerald M. Woods, MD13; Sandra Dixon, MS14; Pratshant Patel, Ph.D.15; Anya D. Nwando, BSc16; Radhika Rana, MSc17; and the Global Blood Therapeutics GBT440 Pediatric Studies Team.

METHODS

Figure 1. Voxelotor: Designed to Bind Hb With High Selectivity

Figure 2. Voxelotor Mechanism of Action: Upstream Interruption of Hbs Polymerization With Potential to Modify Disease

OBJECTIVES

Part A

• To compare the single-dose PK properties of voxelotor in children with those observed in adolescents and adults
• To support dose selection in ongoing studies evaluating the safety and efficacy of voxelotor in children and adolescents
• To select doses for children aged 6-11 years based on PK data and PPK modeling to achieve similar exposures to the 2 doses (900 mg and 1500 mg) that are observed in adolescents and adults

Part B

• To characterize the whole blood and plasma multiple-dose PK of voxelotor in adolescents
• To compare adolescent and adult whole blood and plasma PK

METHODS

Figure 3. Study Design: Dosing Regimen of GBT440-007

RESULTS

It was well tolerated following a single oral dose regimen of voxelotor 400 mg in children (aged 6-11 years) and multiple oral doses (500-1000 mg) in adolescents (aged ≥12 years).

Voxelotor PK Model Description

The voxelotor PK model in children, adolescents, and adults was best described by a 2-compartment model with first-order absorption and first-order elimination of model parameters are summarized in Table 3.

PK Results

• Voxelotor PK exposures in children following single doses of 600 mg were higher than those observed in adolescents (Figure 4 and Table 2)
• Voxelotor concentration profiles in whole blood and plasma in children and adolescents (600 mg and 1500 mg) were described using the 2- and 3-compartment models that described the adult (18 years) concentration profiles (Table 3)
• Voxelotor exposures in children following multiple doses of 900 mg were similar to those observed in adults (Table 2)

• PBPK modeling confirmed the need for lower doses in children (aged 6-11 years) and predicted similar weighted-baseline voxelotor doses (Table 3) in this population

CONCLUSIONS

• Voxelotor was well tolerated following a single oral dose (400 mg) in children (aged 6-11 years) and multiple oral doses (900 and 1500 mg) in adolescents (aged ≥12 years).

Table 2. Whole Blood and Plasma PK Parameters Following a Single Dose of Voxelotor 600 mg in Children and in Adolescents: Noncompartmental PK Analysis

Table 3. Model PPK Parameter Estimates for Children, Adolescents, and Adults With SCD

Table 4. Model Predicted Exposure Estimates for Adolescents and Adults With SCD Following Multiple Doses of 900 mg

Table 5. Voxelotor Projected Doses Selected for Children Aged 6-11y Based on PBPK Modeling and PBPK Modeling

REFERENCES

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DISCLOSURES

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